Published in final edited form as:

Int J Stroke. 2014 January ; 9(1): . doi:10.1111/ijss.12136.

Review of Lipid and Lipoprotein(a) Abnormalities in Childhood Arterial Ischemic Stroke

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Abstract

National organizations recommend cholesterol screening in children to prevent vascular disease in adulthood. There are currently no recommendations for cholesterol and lipoprotein (a) testing in children who experience an arterial ischemic stroke. While dyslipidemia and elevated lipoprotein (a) are associated with ischemic stroke in adults, the role of atherosclerotic risk factors in childhood arterial ischemic stroke is not known. A review of the literature was performed from 1966- 4/2012 to evaluate the association between childhood arterial ischemic stroke and dyslipidemia or elevated lipoprotein (a). Of 239 citations, there were 16 original observational studies in children (with or without neonates,) with imaging-confirmed arterial ischemic stroke and data on cholesterol or lipoprotein (a) values. Three pairs of studies reported overlapping subjects, and 2 were eliminated. Among 14 studies, there was data on cholesterol in 7 and lipoprotein (a) in 10. After stroke, testing was performed at > 3 months in 9 studies, at 3 months in 4 studies and not specified in one study. There were 5 case-control studies: 4 compared elevated lipoprotein (a) and one compared abnormal cholesterol in children with arterial ischemic stroke to controls. A consistent positive association between elevated lipoprotein (a) and stroke was found [Mantel-Haenszel OR 4.24 (2.94–6.11)]. There was no association in one study on total cholesterol, and a positive association in one study on triglycerides. The literature suggests that elevated lipoprotein (a) may be more likely in children with arterial ischemic stroke than in control children. The absence of confirmatory study on dyslipidemia should be addressed with future research.

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Conflicts of interest: none declared

Keywords

childhood stroke; cholesterol; lipid; lipoprotein(a); risk factor; atherosclerosis; review

Introduction

Stroke is a leading cause of childhood disability. Steno-occlusive cerebral arteriopathy is identified in approximately half of children with an arterial ischemic stroke (AIS), the pathophysiology of which is not well understood, but may be associated with infection.(1–4) The majority of acquired cerebral arteriopathy in the adult is attributed to atherosclerotic disease. Atherosclerosis-related risk factors were documented in only 2% of the International Pediatric Stroke Study registry (2003–2007) for childhood AIS but that data was not systematically collected as it was for other risk factors.(5)

Childhood dyslipidemia is a cause of adult atherosclerotic disease. The prospective childhood cohort in Muscatine, Iowa, found that adults with a history of high total cholesterol in childhood were 40–50% more likely to have upper quartile carotid intimal-medial thickness, a marker of atherosclerotic disease.(6) Some atherosclerosis was found in almost all children at autopsy, where death was primary due to trauma, and atherosclerosis was positively associated with non-high-density lipoprotein cholesterol (HDL-c) and negatively associated with HDL cholesterol.(7, 8)

Atherosclerosis is the accumulation of esterified cholesterol within smooth muscle cell.(9) Characteristics of an atherosclerotic plaque are proliferation of smooth muscle cells and intracellular lipid inclusion.(10) In animal study atherosclerosis can be slowly induced with a high fat diet. A high fat diet in the presence of inflammation results in plaque with fatty and proliferative components, typical histologic features of atherosclerosis.(11) The inflammatory state speeds the process of atherosclerosis and leads to diffuse large and small vessel involvement.(12, 13)

On a cellular level, low-density lipoprotein cholesterol (LDL-c) promotes normal cellular division until a threshold dose after which increasing concentrations are cytotoxic. The same effect is not seen with increasing concentrations of HDL-c where a cellular proliferative state continues to a stable threshold.(14) Intracellular LDL-c is tightly regulated by LDL receptor expression, and transmembranous diffusion even at high extracellular concentrations is low. Maximal function of the LDL receptor is seen at interstitial LDL-c levels of 25mg/dL. A higher interstitial level will cause down regulation of receptor expression.(9) Typical human LDL-c interstitial levels are approximately five fold higher than is required by the cell, and the highest of mammalian species, but a normal LDL receptor will continue to optimize intracellular concentrations.(15) When instead LDL-c is in a cationized state, as can occur with inflammation, LDL-c will diffuse freely across the cell membrane.(9)

High Lp(a) is associated with AIS in children and adults.(16, 17) Lp(a) is attached to LDL-c through a disulfide bond, it has athero- and thrombogenic roles and structural similarity with plasminogen.(18–20) Heritability is an important determinant of Lp(a) and it may be more likely elevated in children from families with stroke compared with children from families where there is no history of stroke. (21, 22) Lp(a) has been associated with stroke recurrence in children with AIS.(23) Lp(a) may even be associated dyslipidemia as was found in a sample of Spanish children.(22)

Normative values for cholesterol in childhood are based on population distributions that have evolved historically. Internationally the rate of increase in overweight and obese

children was unprecedented at the turn of this century and prevalence remains at historic high levels.(24–26) Childhood obesity correlates with dyslipidemia.(27) Among adolescents and young adults admitted with stroke in the US Nationwide Inpatient Sample, there was an approximate 4-times increase in the prevalence of lipid disorders between 1995 and 2008. (28) Other US data suggests a trend for increasing incidence of childhood and young adult stroke.(28, 29)

Longstanding atherosclerotic disease as is seen in adults is unlikely to be present in childhood, and without pathologic data, we propose that the pathology of some steno-occlusive arteriopathy in childhood AIS may be atherosclerotic. The aim of this review is to summarize the literature that suggests or supports a role for dyslipidemia and Lp(a) as risk factors or associated factors in childhood AIS.

Methods

Search strategy

An electronic search was performed using Medline via PubMed, OVID, Web of Science and The Cochrane Library, for publications in the English language from 1966 through April 30th 2012, matching a combination of “childhood” or “pediatric” with “lipid,” or “cholesterol”, “dyslipidemia”, or “lipoprotein a” with the term “stroke.” Subject headings and abstracts were reviewed by a single neurologist (SS), for eligibility of data. If potentially appropriate, the study was reviewed in full including the reference list. Of the studies discovered on reference lists, only one additional study contained relevant data.

Selection criteria

Original observational studies in children ($n > 1$), a distinguishable subgroup of children or children with neonates where there was imaging-confirmed AIS, were included if the study contained subject-level or sample distribution values for a cholesterol parameter: total cholesterol (TC), triglycerides (TG), HDL-c, LDL-c or Lp(a). Studies exclusively on neonates were excluded. Early and delayed testing protocols were included.

Five studies that reported performance of lipid testing in children with ischemic stroke were not included. In four studies, the authors commented that there were no lipid abnormalities, but individual or aggregate values were not available for the full sample. (30–34) In the fifth study, modern radiologic evaluation for stroke was not available and the diagnosis of ischemic stroke was not confirmed.(35)

Data extraction

The following data was extracted from relevant studies: country of origin, enrollment dates, year of publication, inclusion and exclusion criteria, study design, number of subjects, age at stroke and lipid or Lp(a) testing, interval to testing, individual or distribution estimates for TC, LDL-c, HDL-c, TG, Lp(a), critical abnormal values, and where available, association estimates with stroke.

Analysis

Review Manager (vs. 5.2, Cochrane IMS) was used to calculate the Mantel-Haenszel odds ratio (MH OR), the Breslow-Day test statistic and to generate the forest plot (Figure 1). The summary MH OR is an estimate of the association of Lp(a) with childhood AIS. The Breslow-Day test of heterogeneity tests the null hypothesis that there is homogeneity of ORs across studies. Estimates for cholesterol data are discussed in relation to National Cholesterol Education Program (NCEP) and American Heart Association (AHA) recommendations for children, where TC should be $< 170 \text{ mg/dL}$, LDL-c $< 110 \text{ mg/dL}$, and

HDL-c >35 mg/dL.(36) There is no standard for a healthy triglyceride level in children, but levels >200mg/dL are associated with obesity.(37) A critical value for Lp(a) of >30mg/dL was accepted based on risk threshold study on childhood venous thromboembolism.(38) International reference for prevalent childhood dyslipidemia (1 lipid abnormality) varies widely and has been estimated at ~20% among 12–19 year olds in the US.(27, 39–41) By cholesterol parameter in this NHANES sample of 12–19 year old children (1999–2006): LDL-c 130 mg/dL was seen in 7.6%; HDL-c 35 mg/dL was seen in 7.6%; and triglycerides 150 mg/dL was seen in 10.2%.(41)

Data reporting

Tables with median and range of lipid values and their association with stroke are used to present the data from 14 studies. These estimates are as reported in the primary study except in one study where individual-level data was available and an estimate for subjects with ischemic stroke was recalculated with exclusion of subjects with hemorrhagic stroke.(42).

Results

An electronic topic search yielded 239 citations. Of these, 15 studies plus one discovered through a reference list contained relevant data. Three pairs of studies were reviewed for overlapping subjects. In the first set, the primary author was contacted and overlap was estimated at less than one third. Both studies are reported with a notation about the overlap in Table 4.(43, 44) A second set consisted of a larger study and subgroup analysis.(45, 46) The larger study was reported.(46) The final set of studies were published in the same year, from the same University hospital, and enrollment dates were not available. The subject number differed by three and there was overlapping authorship.(47, 48) Without a response from the primary authors, the smaller study with fewer estimates was not reported.(47)

Fourteen studies (n= 1,071) are reported in the tables. One study compared TC and TG in children with a history of AIS to controls (Table 1). This study (n_{AIS}=75), found no association between total cholesterol and AIS [OR 1.18 (0.81–1.72)] and a positive association between triglycerides and AIS [OR (2.27–16.20)].(48) Four studies compared Lp(a) values in children with a history of AIS to controls (Figure 1). Each study found a significant positive association between Lp(a) and AIS. A summary MH OR was [4.24 (2.94–6.11)] and study ORs were homogeneous [Breslow-Day Chi-Square 4.59, p= 0.2040].

Among 14 studies, 7 reported data on cholesterol and 10 reported data on Lp(a). Sample frequency data is reported in Tables 2, 3 and 4. The range of study-specific average values in mg/dL for cholesterol parameters: TC (medians 155–166, and a mean of 172), LDL-c (medians 85–101, and mean of 95), HDL-c (medians 47–60, and a mean of 55) and TG (medians 64–88, and a mean of 112), are comparable with NCEP and AHA recommendations.(Table 2)

The range of prevalence (%) estimates for abnormal cholesterol parameters were: TC (9–24), LDL-c (15–20), HDL-c (18–20), and TG (27–30). If we compare these prevalence estimates to population estimates among 12–19 year olds in the US (NHANES) where the threshold for an abnormal value is comparable we find that the population prevalence of high LDL-c (7.6%) appears to be less than in two samples of children with AIS (15% and 19%)(42, 49); that the population prevalence of low HDL-c (7.6%) may be lower than in two samples of children with AIS (18% and 20%)(42, 49); and that the population prevalence of high TG (10.2%) may also be lower than one sample of children with AIS (27%)(49). In a second study with prevalence of abnormal TG, the critical value was lower at 1.4 mmol/L or 124.6mg/dL.(1)(Table 3) The median Lp(a) values (12–15mg/dL) were

below threshold for abnormality ($>30\text{mg/dL}$) but the range of prevalent elevated Lp(a) was appreciable at 18–40%.(Table 4)

There were no studies with lipid testing prior to stroke. In 9 studies, testing for lipid levels was done at > 3 months after the stroke, in 4 studies testing was ≤ 3 months and in one study information on interval to testing was not available. Of 7 studies with cholesterol values, 5(71%) were fasting samples.

Conclusions

This review of the literature confirms an association between Lp(a) and childhood AIS. A recent meta-analysis on thrombophilia in childhood stroke reported a similar pooled OR (6.53, 4.46–9.55).(17) The difference in the pooled ORs between this study and the meta-analysis is due to two additional studies included here(50, 51) and the non-inclusion of two studies used in the meta-analysis because one reported only neonates and the second did not provide the control data in the primary manuscript.(44, 52)

A gap in the literature on dyslipidemia and childhood AIS is noteworthy and is the main limitation in this review. Only a single study compares cases with controls. Other studies report average lipid values and prevalence estimates for abnormal parameter but comparison of these values to external samples has limited validity. There are additional issues with aggregation of estimates from males and females and from a heterogeneous sample of childhood ages. The distribution of cholesterol lipids varies with age and by gender for age. There is a pre-adolescent peak in boys and girls with a subsequent decrease in boys from 12–16 years, not seen in girls this age and return to preadolescent values by late adolescence in boys with continued higher values in girls of the same age.(53, 54) This concern is not shared for Lp(a) values where there is considerably less variability by age and strong heritability.(21)

Aggregating values as proportion abnormal has the advantage of standardization by age and gender. This was done in 2 of 3 studies reporting the prevalence of an abnormal cholesterol parameter. The interpretation of these proportions still requires a reference value and it appeared that abnormal LDL-c, HDL-c and TG values were higher in samples of children with AIS than modern prevalence estimates from adolescents in the US, but this reference population is undoubtedly different from the AIS samples: US (1973–1991), UK (1978–2000) and Austria (1984–2005). Appropriate reference samples would now be difficult to locate.

Another potentially important limitation to the validity of the findings relates to the interval to testing from the time of stroke. Both cholesterol and Lp(a) values have been found to be influenced by an ischemic event. After an acute myocardial infarction, the immediate, 3 and 6 month values are similar to baseline, but in the interval between this time, and by the first hospital day, all lipid concentrations decrease by 15–25% of baseline values.(55–57) Lp(a) similarly drops by 10–25%, but unlike cholesterol, it can rebound on days 7–11 before returning to baseline values by 3 months.(58) This phenomenon has not been studied as extensively after cerebral infarction in adults and has not been studied at all after childhood ischemia. In one adult stroke cohort of Northern Manhattan, serum Lp(a) and other lipid levels obtained within 24 h of acute ischemic stroke did not significantly change at 4 weeks. (59)

The effect of some of these methodological concerns would be to bias the result towards a null effect. Among studies reporting average and prevalence abnormal cholesterol values, the interval from stroke to testing was >3 months in 5/7 (71%) studies. If lipids decrease

after ischemia as is seen after a myocardial infarction these 2 studies report lower than actual values.

The direction of effect for other biases will depend on the specific study methods. A long interval to testing (>12months), noted in 2 studies may include values that are unrelated to lipid metabolism at the time of the stroke. The direction of effect would depend on the relative hormonal and metabolic change at the time of testing. A single estimate obtained by aggregating children with a range of ages will similarly be biased by the age make-up of the sample and the variable contributions of age-related hormonal and metabolic effects. It may be important to analyze childhood data by age categories. The nonlinear trend in cholesterol parameter distribution by age may be associated with a similar nonlinear estimate of risk by age. The expected pre-adolescent cholesterol peak in cholesterol overlaps with the peak in childhood AIS [5.7 years, interquartile range, 1.7–11.6 years], reported from the International Pediatric Stroke Study registry (2003–2007).(5)

Like age, certain subgroups of children with AIS having other risk factors may have a higher risk of stroke with dyslipidemia than other subgroups. In many of the studies presented here the authors excluded children with AIS who additionally had one of a list of other risk factors. The original desire for this may have been to study dyslipidemia as an independent risk factor, but as the literature on childhood AIS expands we are learning that multiple risk factors are the norm, such as a recent study showing an association between cardio-embolic stroke and recent infection.(60) If dyslipidemia is a risk factor only as it interacts with other risk factors, such as an infectious or inflammatory state, the selection of a sample of children with AIS and few or no other identified risk factors, will have no association with stroke.

The single case control study on cholesterol deserves particular mention because as this would otherwise be considered the best source of evidence there are a number of concerns in the study design where the effect of bias would be towards a null association. Control subjects were older and pre-pubertal (mean age 10.3 versus 8.2 in cases) and more likely female (69% versus 59% among cases). Both of these differential demographics of the control group would result in higher cholesterol in the control group. Unfortunately information on interval to testing was not available which further limits the value that can be placed on their findings.(48)

In December, 2011 the National Heart, Lung, and Blood Institute (NHLBI) with American Academy of Pediatrics (AAP) endorsement, recommended universal lipid screening for children at 9 to 11 years of age and again at 17 to 21 years of age.(61) The most recent, 2008 AHA guidelines on the management of stroke in infants and children does not discuss testing lipids. (62) In keeping with previous literature, our review suggests an association between high Lp(a) and childhood AIS. Niacin is effective at lowering Lp(a) levels,(63) but there is currently no data demonstrating that niacin reduces the risk of stroke.(64, 65) On the other hand, modification of dyslipidemia positively impacts secondary stroke prevention in adults.(66) Randomized controlled study on statin use in children with hyperlipidemia has demonstrated efficacy and safety.(67–69)

An ongoing prospective study, the Vascular Effects of Infection in Pediatric Stroke (VIPS) study, will test the association between infection, childhood AIS and arteriopathy.(4) Four of the studies presented here discuss a vascular abnormality (stenosis or occlusion) in their cohort but the data was not available to correlate dyslipidemia with arteriopathy.(1, 46, 49, 70) Further exploration of the role of dyslipidemia in childhood stroke could not only identify a modifiable risk factor but could shed light into the pathophysiology of arteriopathy. The diverse properties of statins may be especially beneficial if there is an athero-inflammatory process involved in childhood AIS with arteriopathy. The biologic

plausibility and failure of the past literature to demonstrate no association are cause for future research on dyslipidemia in childhood AIS.

Future study should be designed with the limitations of these historic studies in mind. An appropriate reference group is necessary to estimate the effect size and there should be group or individual-level matching by age category and gender to limit confounding by these variables. In order to learn about how dyslipidemia might interact with other risk factors, a study design should include all childhood AIS with accounting for major risk factor categories in the demographics and analysis. A case-control design using an available large research cohort of childhood AIS with demographic and stroke risk factor information is ideally suited to provide evidence for an association. Still anticipated limitations to such a study are an absence of uniform lipid testing in an existing cohort and variability in the interval to testing. It will be necessary to compare the sub-cohort that is tested to the untested sub-cohort and account for biases in testing in the final analysis. The interval to testing should also be categorized (i.e. <24 hours, 24 hours-1 week, >1 week-3 months, >3months- 6months) and data analyzed by testing interval. Future prospective testing in a childhood cohort identified rapidly after stroke with testing at (i.e. <24 hours; 24 hours, 7 days; 14 days; 3 months and 6 months) and prospective follow-up for stroke recurrence would be positioned to estimate the association between dyslipidemia and AIS, to assess risk of a recurrence stroke due to dyslipidemia and to address the influence of a stroke on lipid values in children.

Acknowledgments

Funding: Sally Sultan, NIH-T32-NS07153

References

1. Ganesan V, Prengler M, McShane MA, Wade AM, Kirkham FJ. Investigation of risk factors in children with arterial ischemic stroke. *Ann Neurol*. 2003 Feb; 53(2):167–73. [PubMed: 12557282]
2. Dlamini N, Freeman JL, Mackay MT, Hawkins C, Shroff M, Fullerton HJ, et al. Intracranial dissection mimicking transient cerebral arteriopathy in childhood arterial ischemic stroke. *J Child Neurol*. 2011 Sep; 26(9):1203–6. [PubMed: 21743063]
3. Amlie-Lefond C, Bernard TJ, Sebire G, Friedman NR, Heyer GL, Lerner NB, et al. Predictors of cerebral arteriopathy in children with arterial ischemic stroke: results of the International Pediatric Stroke Study. *Circulation*. 2009 Mar 17; 119(10):1417–23. [PubMed: 19255344]
4. Fullerton HJ, Elkind MS, Barkovich AJ, Glaser C, Glidden D, Hills NK, et al. The vascular effects of infection in Pediatric Stroke (VIPS) Study. *J Child Neurol*. 2011 Sep; 26(9):1101–10. [PubMed: 21616922]
5. Mackay MT, Wiznitzer M, Benedict SL, Lee KJ, Deveber GA, Ganesan V. Arterial ischemic stroke risk factors: the International Pediatric Stroke Study. *Ann Neurol*. 2011 Jan; 69(1):130–40. [PubMed: 21280083]
6. Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. *Circulation*. 2001 Dec 4; 104(23):2815–9. [PubMed: 11733400]
7. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med*. 1998 Jun 4; 338(23):1650–6. [PubMed: 9614255]
8. McGill HC Jr, McMahan CA, Malcom GT, Oalmann MC, Strong JP. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women. The PDAY Research Group. Pathobiological Determinants of Atherosclerosis in Youth. *Arterioscler Thromb Vasc Biol*. 1997 Jan; 17(1):95–106. [PubMed: 9012643]
9. Goldstein JL, Brown MS. The low-density lipoprotein pathway and its relation to atherosclerosis. *Annu Rev Biochem*. 1977; 46:897–930. [PubMed: 197883]

10. Schwartz CJ, Mitchell JR. The morphology, terminology and pathogenesis of arterial plaques. *Postgrad Med J.* 1962 Jan;38:25–34. [PubMed: 13909683]
11. Kritchevsky D, Tepper SA, Kim HK, Moses DE, Story JA. Experimental atherosclerosis in rabbits fed cholesterol-free diets. 4. Investigation into the source of cholesteremia. *Exp Mol Pathol.* 1975 Feb; 22(1):11–9. [PubMed: 1116563]
12. Minick CR, Murphy GE, Campbell WG Jr. Experimental induction of athero-arteriosclerosis by the synergy of allergic injury to arteries and lipid-rich diet. I. Effect of repeated injections of horse serum in rabbits fed a dietary cholesterol supplement. *J Exp Med.* 1966 Oct 1; 124(4):635–52. [PubMed: 5922287]
13. Van Winkle M, Levy L. Effect of removal of cholesterol diet upon serum sickness-cholesterol-induced atherosclerosis. *J Exp Med.* 1968 Sep 1; 128(3):497–515. [PubMed: 5666961]
14. Tauber JP, Cheng J, Gospodarowicz D. Effect of high and low density lipoproteins on proliferation of cultured bovine vascular endothelial cells. *J Clin Invest.* 1980 Oct; 66(4):696–708. [PubMed: 7419717]
15. Mills GL, Taylaur CE. The distribution and composition of serum lipoproteins in eighteen animals. *Comp Biochem Physiol B.* 1971 Oct; 40(2):489–501. [PubMed: 5000981]
16. Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA.* 2009 Jul 22; 302(4):412–23. [PubMed: 19622820]
17. Kenet G, Lutkhoff LK, Albisetti M, Bernard T, Bonduel M, Brandao L, et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. *Circulation.* 2010 Apr 27; 121(16):1838–47. [PubMed: 20385928]
18. Utermann G. The mysteries of lipoprotein(a). *Science.* 1989 Nov 17; 246(4932):904–10. [PubMed: 2530631]
19. Scanu AM, Fless GM. Lipoprotein (a). Heterogeneity and biological relevance. *J Clin Invest.* 1990 Jun; 85(6):1709–15. [PubMed: 2140835]
20. Marcovina SM, Koschinsky ML. Evaluation of lipoprotein(a) as a prothrombotic factor: progress from bench to bedside. *Curr Opin Lipidol.* 2003 Aug; 14(4):361–6. [PubMed: 12865733]
21. Chunsheng L, Cai L, Aimin L, Rongbin Z, Xiulan G. A correlative study on serum Lp(a) in patients of cerebral infarction with that in their children. *Chin Med Sci J.* 1999 Dec.14(4):232. [PubMed: 12894898]
22. Gonzalez-Requejo A, Sanchez-Bayle M, Ruiz-Jarabo C, Asensio-Anton J, Pelaez MJ, Morales MT, et al. Lipoprotein(a) and cardiovascular risk factors in a cohort of 6-year-old children. The Rivas-Vaciamadrid Study. *Eur J Pediatr.* 2003 Sep; 162(9):572–5. [PubMed: 12819963]
23. Strater R, Becker S, von Eckardstein A, Heinecke A, Gutsche S, Junker R, et al. Prospective assessment of risk factors for recurrent stroke during childhood--a 5-year follow-up study. *Lancet.* 2002 Nov 16; 360(9345):1540–5. [PubMed: 12443591]
24. van den Hurk K, van Dommelen P, van Buuren S, Verkerk PH, Hirasing RA. Prevalence of overweight and obesity in the Netherlands in 2003 compared to 1980 and 1997. *Arch Dis Child.* 2007 Nov; 92(11):992–5. [PubMed: 17604303]
25. Bundred P, Kitchiner D, Buchan I. Prevalence of overweight and obese children between 1989 and 1998: population based series of cross sectional studies. *BMJ.* 2001 Feb 10; 322(7282):326–8. [PubMed: 11159654]
26. Parrino C, Rossetti P, Baratta R, La Spina N, La Delfa L, Squatrito S, et al. Secular trends in the prevalence of overweight and obesity in Sicilian schoolchildren aged 11–13 years during the last decade. *PLoS One.* 2012; 7(4):e34551. [PubMed: 22506027]
27. Martinson ML, Teitler JO, Reichman NE. Health across the life span in the United States and England. *Am J Epidemiol.* 2011 Apr 15; 173(8):858–65. [PubMed: 21389038]
28. George MG, Tong X, Kuklina EV, Labarthe DR. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995–2008. *Ann Neurol.* 2011 Nov; 70(5):713–21. [PubMed: 21898534]

29. Gandhi SK, McKinney JS, Sedjro JE, Cosgrove NM, Cabrera J, Kostis JB. Temporal trends in incidence and long-term case fatality of stroke among children from 1994 to 2007. *Neurology*. 2012 May 30.
30. Obama MT, Dongmo L, Nkemayim C, Mbede J, Hagbe P. Stroke in children in Yaounde, Cameroon. *Indian Pediatr*. 1994 Jul; 31(7):791–5. [PubMed: 7890341]
31. Dusser A, Goutieres F, Aicardi J. Ischemic strokes in children. *J Child Neurol*. 1986 Apr; 1(2): 131–6. [PubMed: 3598117]
32. Janaki S, Baruah JK, Jayaram SR, Saxena VK, Sharma SH, Gulati MS. Stroke in the young: a four-year study, 1968 to 1972. *Stroke*. 1975 May-Jun;6(3):318–20. [PubMed: 1154468]
33. Blennow G, Cronqvist S, Hindfelt B, Nilsson O. On cerebral infarction in childhood and adolescence. *Acta Paediatr Scand*. 1978 Jul; 67(4):469–75. [PubMed: 676733]
34. Giroud M, Lemesle M, Madinier G, Manceau E, Osseby GV, Dumas R. Stroke in children under 16 years of age. Clinical and etiological difference with adults. *Acta Neurol Scand*. 1997 Dec; 96(6):401–6. [PubMed: 9449480]
35. Scheffner D, Willie L. Acute infantile hemiplegia due to obstruction of intracranial arterial vessels. *Neuropadiatrie*. 1973 Jan; 4(1):7–19. [PubMed: 4739779]
36. American Academy of Pediatrics. National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 1992 Mar; 89(3 Pt 2): 525–84. [PubMed: 1538956]
37. Williams CL, Hayman LL, Daniels SR, Robinson TN, Steinberger J, Paridon S, et al. Cardiovascular health in childhood: A statement for health professionals from the Committee on Atherosclerosis, Hypertension, and Obesity in the Young (AHOY) of the Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation*. 2002 Jul 2; 106(1):143–60. [PubMed: 12093785]
38. Nowak-Gottl U, Junker R, Hartmeier M, Koch HG, Munchow N, Assmann G, et al. Increased lipoprotein(a) is an important risk factor for venous thromboembolism in childhood. *Circulation*. 1999 Aug 17; 100(7):743–8. [PubMed: 10449697]
39. Krawczyk M, Czarniak P, Szczesniak P, Krol E, Pakalska Korcala A, Kusiak A, et al. The prevalence of risk factors for atherosclerosis among middle school students in Sopot, Poland: results of the SOPKARD 15 programme. *Kardiol Pol*. 2011; 69(6):540–5. [PubMed: 21678286]
40. Magkos F, Manios Y, Christakis G, Kafatos AG. Secular trends in cardiovascular risk factors among school-aged boys from Crete, Greece, 1982–2002. *Eur J Clin Nutr*. 2005 Jan; 59(1):1–7. [PubMed: 15383826]
41. CDC. Prevalence of Abnormal Lipid Levels Among Youths - United States, 1999–2006. 2010; 59(02):29–33.
42. Simma B, Martin G, Muller T, Huemer M. Risk factors for pediatric stroke: consequences for therapy and quality of life. *Pediatr Neurol*. 2007 Aug; 37(2):121–6. [PubMed: 17675027]
43. Normann S, de Veber G, Fobker M, Langer C, Kenet G, Bernard TJ, et al. Role of endogenous testosterone concentration in pediatric stroke. *Ann Neurol*. 2009 Dec; 66(6):754–8. [PubMed: 20033984]
44. Nowak-Gottl U, Langer C, Bergs S, Thedieck S, Strater R, Stoll M. Genetics of hemostasis: differential effects of heritability and household components influencing lipid concentrations and clotting factor levels in 282 pediatric stroke families. *Environ Health Perspect*. 2008 Jun; 116(6): 839–43. [PubMed: 18560491]
45. Daniels SR, Bates S, Lukin RR, Benton C, Third J, Glueck CJ. Cerebrovascular arteriopathy (arteriosclerosis) and ischemic childhood stroke. *Stroke*. 1982 May-Jun;13(3):360–5. [PubMed: 7080131]
46. Glueck CJ, Daniels SR, Bates S, Benton C, Tracy T, Third JL. Pediatric victims of unexplained stroke and their families: familial lipid and lipoprotein abnormalities. *Pediatrics*. 1982 Mar; 69(3): 308–16. [PubMed: 6977760]
47. Balcerzyk A, Zak I, Niemiec P, Kopyta I, Emich-Widera E, Iwanicki T, et al. APOE gene epsilon polymorphism does not determine predisposition to ischemic stroke in children. *Pediatr Neurol*. 2010 Jul; 43(1):25–8. [PubMed: 20682199]

48. Kopyta I, Sarecka-Hujar B, Emich-Widera E, Marszał E, Zak I. Association between lipids and fibrinogen levels and ischemic stroke in the population of the Polish children with arteriopathy and cardiac disorders. *Wiad Lek.* 2010; 63(1):17–23. [PubMed: 20701026]
49. Abram HS, Knepper LE, Warty VS, Painter MJ. Natural history, prognosis, and lipid abnormalities of idiopathic ischemic childhood stroke. *J Child Neurol.* 1996 Jul; 11(4):276–82. [PubMed: 8807416]
50. Beheiri A, Langer C, During C, Krumpel A, Thedieck S, Nowak-Gottl U. Role of elevated alpha2-macroglobulin revisited: results of a case-control study in children with symptomatic thromboembolism. *J Thromb Haemost.* 2007 Jun; 5(6):1179–84. [PubMed: 17403113]
51. Teber S, Deda G, Akar N, Soylu K. Lipoprotein (a) levels in childhood arterial ischemic stroke. *Clin Appl Thromb Hemost.* 2010 Apr; 16(2):214–7. [PubMed: 19752039]
52. Kurnik K, Kosch A, Strater R, Schobess R, Heller C, Nowak-Gottl U. Recurrent thromboembolism in infants and children suffering from symptomatic neonatal arterial stroke: a prospective follow-up study. *Stroke.* 2003 Dec; 34(12):2887–92. [PubMed: 14631084]
53. Skinner AC, Steiner MJ, Chung AE, Perrin EM. Cholesterol curves to identify population norms by age and sex in healthy weight children. *Clin Pediatr (Phila).* 2012 Mar; 51(3):233–7. [PubMed: 22157422]
54. Brotons C, Ribera A, Perich RM, Abrodo D, Magana P, Pablo S, et al. Worldwide distribution of blood lipids and lipoproteins in childhood and adolescence: a review study. *Atherosclerosis.* 1998 Jul; 139(1):1–9. [PubMed: 9699886]
55. Ahnve S, Angelin B, Edhag O, Berglund L. Early determination of serum lipids and apolipoproteins in acute myocardial infarction: possibility for immediate intervention. *J Intern Med.* 1989 Nov; 226(5):297–301. [PubMed: 2809505]
56. Fyfe T, Baxter RH, Cochran KM, Booth EM. Plasma-lipid changes after myocardial infarction. *Lancet.* 1971 Nov; 2(7732):997–1001. [PubMed: 4108108]
57. Stubbe I, Gustafson A, Nilsson-Ehle P. Alterations in plasma proteins and lipoproteins in acute myocardial infarction: effects on activation of lipoprotein lipase. *Scand J Clin Lab Invest.* 1982 Sep; 42(5):437–44. [PubMed: 7156856]
58. Andreassen AK, Berg K, Torsvik H. Changes in Lp(a) lipoprotein and other plasma proteins during acute myocardial infarction. *Clin Genet.* 1994 Dec; 46(6):410–6. [PubMed: 7534219]
59. Kargman DE, Tuck C, Berglund L, Lin IF, Mukherjee RS, Thompson EV, et al. Lipid and lipoprotein levels remain stable in acute ischemic stroke: the Northern Manhattan Stroke Study. *Atherosclerosis.* 1998 Aug; 139(2):391–9. [PubMed: 9712347]
60. Rodan L, McCrindle BW, Manlhiot C, Macgregor DL, Askalan R, Moharir M, et al. Stroke recurrence in children with congenital heart disease. *Ann Neurol.* 2012 Jul; 72(1):103–11. [PubMed: 22829272]
61. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics.* 2011 Dec; 128(Suppl 5):S213–56. [PubMed: 22084329]
62. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G, et al. Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. *Stroke.* 2008 Sep; 39(9):2644–91. [PubMed: 18635845]
63. Carlson LA, Hamsten A, Asplund A. Pronounced lowering of serum levels of lipoprotein Lp(a) in hyperlipidaemic subjects treated with nicotinic acid. *J Intern Med.* 1989 Oct; 226(4):271–6. [PubMed: 2530298]
64. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med.* 2011 Dec 15; 365(24):2255–67. [PubMed: 22085343]
65. Nicholls SJ. Is niacin ineffective? Or did AIM-HIGH miss its target? *Cleve Clin J Med.* 2012 Jan; 79(1):38–43. [PubMed: 22219232]
66. Bernard TJ, Manco-Johnson MJ, Lo W, MacKay MT, Ganesan V, DeVeber G, et al. Towards a consensus-based classification of childhood arterial ischemic stroke. *Stroke.* 2012 Feb; 43(2):371–7. [PubMed: 22156694]

67. Wiegman A, Hutten BA, de Groot E, Rodenburg J, Bakker HD, Buller HR, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA*. 2004 Jul 21; 292(3):331–7. [PubMed: 15265847]
68. van der Graaf A, Nierman MC, Firth JC, Wolmarans KH, Marais AD, de Groot E. Efficacy and safety of fluvastatin in children and adolescents with heterozygous familial hypercholesterolaemia. *Acta Paediatr*. 2006 Nov; 95(11):1461–6. [PubMed: 17062478]
69. Gandelman K, Glue P, Laskey R, Jones J, LaBadie R, Ose L. An eight-week trial investigating the efficacy and tolerability of atorvastatin for children and adolescents with heterozygous familial hypercholesterolemia. *Pediatr Cardiol*. 2011 Apr; 32(4):433–41. [PubMed: 21259004]
70. Strater R, Vielhaber H, Kassenbohmer R, von Kries R, Gobel U, Nowak-Gottl U. Genetic risk factors of thrombophilia in ischaemic childhood stroke of cardiac origin. A prospective ESPED survey. *Eur J Pediatr*. 1999 Dec; 158(Suppl 3):S122–5. [PubMed: 10650850]
71. Nowak-Gottl U, Strater R, Heinecke A, Junker R, Koch HG, Schuierer G, et al. Lipoprotein (a) and genetic polymorphisms of clotting factor V, prothrombin, and methylenetetrahydrofolate reductase are risk factors of spontaneous ischemic stroke in childhood. *Blood*. 1999 Dec 1; 94(11):3678–82. [PubMed: 10572079]
72. Nowak-Gottl U, Debus O, Findeisen M, Kassenbohmer R, Koch HG, Pollmann H, et al. Lipoprotein (a): its role in childhood thromboembolism. *Pediatrics*. 1997 Jun; 99(6):E11. [PubMed: 9164807]
73. Lynch JK, Han CJ, Nee LE, Nelson KB. Prothrombotic factors in children with stroke or porencephaly. *Pediatrics*. 2005 Aug; 116(2):447–53. [PubMed: 16061602]
74. Barreirinho S, Ferro A, Santos M, Costa E, Pinto-Basto J, Sousa A, et al. Inherited and acquired risk factors and their combined effects in pediatric stroke. *Pediatr Neurol*. 2003 Feb; 28(2):134–8. [PubMed: 12699865]

Figure 1.
Association between abnormal Lp(a) and AIS

Table 1

Odds Ratio for Cholesterol and Triglyceride

Author	Subjects (n _{abnormal} /n _{total})	Controls (n _{abnormal} /n _{total})	Delayed testing	TC: OR, 95%CI, p value	TG: OR, 95%CI, p value
Kopyta I. et al.(48)	NA/75	NA/71	NA	1.18 (0.81–1.72), 0.39	6.06 (2.27–16.20), <0.001

NA=not available

Summary cholesterol parameters

Table 2

Author	Country	Enrollment period	Included (N=neonate, C=Child)	Excluded	Number of subjects w/AIS	Number of subjects tested	Age (yrs) at time of stroke	Age range of stroke (yrs)	Age range at time of testing (yrs)	Delayed testing (months)	Fasted	TC (mg/dL) median (range)	LDL-C (mg/dL) median (range)	HDL-C (mg/dL) median (range)	TG (mg/dL) median (range)	Study design/comment
Normal reference values (NCEP and AHA)																
Kopyta L., et al. (48)	Poland	NA (published 2010)	C	-	75	75	8.2	0.75–17	0.8–18	NA	yes	171.7 (32.9) mean (SD)	94.7 (34.8) mean (SD)	54.5 (27.8) mean (SD)	111.6 (32.8) mean (SD)	case control (association of lipids with stroke)
Normann S., et al. (43)	Germany	1/2004–1/2009	N+C	-	72	72	5	term-18	0.5–18	6–12	yes	155 (110–336)	-	-	-	case control (association of lipids with testosterone)
Nowak-Göttl U., et al.(44)	Germany	7/1996–8/2006	N+C	-	282	282	4 (age at testing)	NA	0.1–18	6–12	yes	161 (91–249)	85 (24–177)	55 (25–104)	-	cross sectional (correlation in families)
Abram HS., et al.(49)	US	1973–1991	C	head trauma, cardiac, hematologic & metabolic disorders	42	TC 41; LDL 37; HDL 38; TG 41	6	0.75–18	2.0–33	12–234	yes (excl. 5)	166 (116–182)	101 (60–121)	47 (34–88)	64 (26–139)	case series (risk factors for poor outcome)
Glueck CJ., et al. (46)	US	1968–1982	C	Identified cause of stroke	11	11	7	1.25–17	1.33–21	>6	yes	158 (120–204)	97 (40–123)	60 (46–63)	88 (60–121)	cross sectional (correlation in families)

NA=not available

* no recommended value (<200 from obesity literature)

Proportion abnormal by cholesterol parameter

Table 3

Author	Country	Excluded	TC, ratio (%)	LDL-C ratio (%)	HDL-C ratio (%)	TG ratio (%)	Critical values	Delayed testing (months)	Fasting	Study design/comment
Reference values NHANES (12–19 years 1999–2006)(41)										
Abram HS., et al. (49)	US	head trauma, cardiac, hematologic& metabolic disorders	10/41 (24)	7/37 (19)	7/38 (18)	11/41 (27)	age and sex %tile; >90th TG, TC, and LDL-C; < 10th HDL-C *	12–234	yes	case series, risk factors for poor outcome
Ganesan V., et al. (1)	UK	congenital hemiplegia & silent infarction	10/117(9)	-	-	36/117 (31)	TC >5.4mmol/L (>210mg/dL); TG >1.4micromol/L **	acute	no	retrospective, comparison of risk factors in stroke subgroups
Simma B. et al. (42)	Austria	porencephaly & head injury	borderline 5/15 (33), absolute 2/15 (15)	borderline 3/15 (20), absolute 2/15 (15)	3/15 (20)		“Age-related values” Ref.[Borderline TC: 170–199 mg/dL and LDL-c 110–129 mg/dL; High TC 200 mg/dL and LDL-c 130 mg/dL]	4.8–216	no	retrospective, descriptive

* This is equivalent to the reference values used for 12–19 year olds in the NHANES analysis.

** 1.4 μmol/L is as reported in the original study however 1.4 mmol/L (=124.6mg/dL) is a common threshold value.

Summary Lipoprotein(a)

Table 4

Author	Country	Enrollment dates	Inclusion (N=neonate, C=Child)	Excluded	Number of subjects w/AIS	Number of subjects tested	Age (yrs) at stroke, median, range	Delayed testing (months)	Lp(a) > 30 mg/dL (%)	Lp(a) (mg/dL), median, range	Study design/comment
Nowak-Göttl U., et al.(72)	Germany	1992–1996	N+C	-	36	36	birth–18	acute and >6	²² (Lp(a)>50mg/dL on repeated testing)	15 (0–145)	case series (prevalence of risk factors)
Nowak-Göttl U., et al.(71)	Germany	10/1995–10/1998	C	Cardiac, infectious, collagen vascular and metabolic disorders, cerebral vasculopathy	148	148	4.5 (0.5–16)	1.5–3	26.4*		case control (association of Lp(a) with stroke)
Sträter R, et al.(70)	Germany	10/1995–10/1998	N+C	Non-cardiac disease	38	38	neonate–18	NA	18.4		case control (association of Lp(a) with stroke)
Nowak-Göttl U., et al.(44)	Germany	7/1996–8/2006	N+C	-	282	282	4 (0.1–18)(age at blood collection)	6–12	25.5*	14 (0–168)	cross sectional (correlation in families)
Ganesan V., et al.(1)	UK	1978–2000	N+C	congenital hemiplegia, and silent infarction	212	41	5 (21 days-19.7)	acute	22		retrospective, comparison of risk factors in stroke subgroups
Beheiri A., et al.(50)	Germany	01/2002 and 12/2004	N+C	cerebral vascular disease	103	103	4 (1–15) (age at blood collection)	12–18	29.1		case control (association of Lp(a) with stroke)
Teber S, et al.(51)	Turkey	1/1992–2/2006	N+C	-	52	52	3.2 +/- 4.4 (mean, SD) ; range(0–15)	3–6	26.9	11.9 (1.9–140)	case control (association of Lp(a) with stroke)
Lynch JK, et al.(73)	US	1990–2000	N+C	Cardiac, chromosomal, metabolic or hematologic disease and history of cancer, trauma, or CNS infection	59	59	0.67 (1 day-12)	> 3	20.3		case series (prevalence of risk factors and comparison with published rates)
Simma B, et al.(42)	Austria	1984–2005	C	porencephaly, head injury	15	15	6 (0.9–14)	4–216	40		retrospective, descriptive
Barreirinho S, et al.(74)	Portugal	1987–1999	C	-	21	21	4.5 (0.17–13)	acute	28.6		prevalence of Lp(a)(case control for other inherited risk factors)

* overlapping subjects